SUMMARY OF SAFETY AND EFFECTIVENESS

1.General Information

Device Generic Name:	Implantable Pacemaker Pulse Generator
Device Trade Name:	Medtronic AT500™ DDDRP Pacing System (Model AT501) Medtronic AT500™ DDDRP Pacing System (Model 9968) Software
Applicant's Name and Address:	Medtronic, Inc. 710 Medtronic Parkway NE Minneapolis, MN 55432-5604
Premarket Approval (PMA) Application Number:	P980035/S13
Date of Panel Recommendation	None
Date of Notice of Approval to the Applicant:	March 26, 2003

II.Indications for Use

The Medtronic AT500 DDDRP pacing system is indicated for the following:

- Rate adaptive pacing in patients who may benefit from increased pacing rates concurrent with increases in activity.
- Accepted patient conditions warranting chronic cardiac pacing which include:
  - Symptomatic paroxysmal or permanent second or third-degree AV block.
  - Symptomatic bilateral bundle branch block.
  - Symptomatic paroxysmal or transient sinus node dysfunctions with or without associated AV conduction disorders.
  - Bradycardia-tachycardia syndrome to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmias.

The Medtronic AT500 system is also indicated for dual chamber and atrial tracking modes in patients who may benefit from maintenance of AV synchrony. Dual chamber modes are specifically indicated for treatment of conduction disorders that require restoration of both rate and AV synchrony, which include:

- Various degrees of AV block to maintain the atrial contribution to cardiac output.
- VVI intolerance (e.g., pacemaker syndrome) in the presence of persistent sinus rhythm.

Antitachycardia pacing (ATP) is indicated for termination of atrial tachyarrhythmias in bradycardia patients with one or more of the above pacing indications.

Atrial rhythm management features such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive Pacing (PMOP) are indicated for the suppression of atrial tachyarrhythmias in bradycardia patients with atrial septal lead placement and one or more of the above pacing indications.

V.Device Description

The Medtronic AT500 DDDRP pacing system is a dual chamber, rate responsive implantable pulse generator (IPG) and is labeled for patients having standard bradycardia indications. The AT500 also contains Atrial Anti-Tachycardia Pacing therapies. In addition, atrial pacing features are provided to further control atrial rates either through increased atrial pacing, rate stabilization, or overdrive pacing post mode switch.

By means of the InCheck™ Model 9465 Patient Assistant[1], the patient can verify whether the device has detected a suspected atrial arrhythmia and initiate recording of cardiac event data in the device memory.

The Medtronic programmer (Model 9790/C or Model 2090[2]), Model 9968 software, and a telemetry programming head constitute the external portion of the DDDRP pacing system. Programmers from other manufacturers are not compatible.

[1] P980050/S02, Approved 13 February 2001

[2] P890003/S36, Approved 31 July 1995, P890003/S44, Approved 21 May 1998 and 2090-P890003, S65, Approved 13 March 2002

Overview Of Features

The AT500 contains bradycardia pacemaker features and in addition, includes the following atrial pacing features and atrial arrhythmia termination therapy:

Atrial Pacing Features

Atrial Preference Pacing (APP)

This feature attempts to achieve the maximum amount of atrial pacing while the patient is not in an atrial arrhythmia. Changes to the pacing interval are made after non-refractory atrial senses affecting a stair-step increase in the pacing interval. Changes to the pacing interval are also made after a consecutive number of atrial paces have been delivered in which case the pacing rate is decreased. APP is available in DDD, DDDR, AAI, and AAIR modes.

Atrial Rate Stabilization (ARS)

This feature is a programmable parameter designed to inhibit the onset of atrial tachyarrhythmias by eliminating the long pause that typically follows a premature atrial contraction (PAC). This feature is similar to that approved in the Jewel AF.[3]

Post Mode Switch Overdrive Pacing (PMOP)

This is a feature that can be used to effect high-rate overdrive DDIR pacing after an atrial tachyarrhythmia episode has terminated. This is accomplished by programming a high Overdrive Rate and an appropriately long Overdrive Period. This feature is similar to that approved in the Jewel AF.

AT Termination Therapy

Up to three automatic antitachycardia pacing AT therapies can be delivered. Ventricular backup pacing during the ATP sequence is available for patients with a high degree of AV Block. There is a programmable delay between preliminary detection and therapy delivery:

- Atrial Anti-Tachycardia Pacing (ATP)
  - A-Ramp protocol
  - A-Burst + protocol
- Manual 50Hz High Frequency Burst

[3] Jewel AF, Model 7250 (P980050, Approved 14 June 2000)

These features are identical to the Jewel AF Model 7250, with the exception of the addition of the VVI backup option. The VVI backup pacing does not affect the ATP therapy in any way.

The AT500 analyzes the timing and pattern of sensed events in the atrium and ventricle to detect AF and AT. It also applies this analysis to monitor for non-sustained ventricular arrhythmia episodes. Based on patterns of atrial and ventricular events, and the timing relationships between these events, the DDDRP pacing system classifies arrhythmias into atrial and ventricular episodes.

When an atrial arrhythmia is detected as stable (such as flutter or tachycardia - the device classifies these both as AT), the DDDRP pacing system automatically delivers antitachycardia pacing (when enabled) after the physician-programmed duration has expired. No pacing therapies are available for episodes that the device classifies as AF. An episode can change classifications as the rhythm of the episode changes – for example, an arrhythmia initially classified as AF and then change to AT, or vice versa. In this case, antitachy pacing is delivered whenever the rhythm currently is classified AT and the delivery criteria are met.

Arrhythmia and Symptom Monitoring

Patients may use a hand-held assistant device to create a log in the device that documents when they felt symptomatic.

The AT500 uses its extensive memory to store information about arrhythmias. Diagnostic information available includes electrograms of specific episodes and long-term clinical trend information about daily arrhythmia incidence for the past two years.

Other Features

Atrial 50Hz High Frequency Burst (HFB)

A-50 Hz burst is available as a therapy to terminate AF or AT. The therapy works by depolarizing cardiac tissue, which has just repolarized, preventing sustained reentry. The AT500 has the A-50Hz Burst available as an In Clinic Only feature, to be available in a physician-controlled environment only. This feature is identical to that in the Jewel AF Model 7250.

Atrial Lead Position Check

Each night at midnight, the device checks for an atrial lead dislodgement to prevent the delivery of atrial antitachycardia therapy when the atrial lead position is not judged to be appropriate. The atrial pacing amplitudes are increased from the brady settings to the settings used for antitachy pacing. The device monitors for the next 256 ventricular events. If it sees 4 instances of atrial pace followed by rapid ventricular sense (within 80ms), the device disables antitachy pacing. No change in therapy occurs during the test so patients should be unaware of its operation.

System Description

The Medtronic AT500 DDDRP Pacing system consists of the Medtronic Model AT501 (to be referred to as "AT500", where appropriate) and the additional components listed below:

InCheck™ AT Model 9465 Patient Assistant[4]

The InCheck AT Patient Assistant is a hand-held, battery-operated, communicator and may be prescribed for a patient by their physician for use in enabling preprogrammed implantable devices capable of detecting and/or treating atrial arrhythmias.

The Model 9465 is intended to be used with existing and future devices. Dependent upon the implanted device, the functions of this device are to:

- Enable patient-activated, physician-programmed atrial therapy (cardioversion) for atrial arrhythmias if an atrial arrhythmia is present (The AT500 is not capable of this function),
- Provide query capability of the implanted device regarding the presence of atrial arrhythmias for the patient,
- Store dates and times within the implanted device, along with relevant data, when the patient is experiencing symptomatic events.

Model 9790/C and 2090 Programmer

These programmer families are used as a user interface for interrogating the AT500 and for collection of data as needed.

Model 9968 Software

The Model 9968 software will be used to support the AT500.

III.Contraindications

The Medtronic AT500 DDDRP pacing system is contraindicated for:

- Implantation with unipolar pacing leads.
- Concomitant implantation with another bradycardia device.
- Concomitant implantation with an implantable cardioverter defibrillator.

[4] P980050/S02, Approved 13 February 2001

There are no known contraindications for the use of pacing as a therapeutic modality to control heart rate. The patient's age and medical condition, however, may dictate the particular pacing system, mode of operation, and implantation procedure used by the physician.

- Rate responsive modes may be contraindicated in those patients who cannot tolerate pacing rates above the programmed Lower Rate.
- Dual chamber sequential pacing is contraindicated in patients with chronic or persistent supraventricular tachycardias, including atrial fibrillation or flutter.
- Single chamber atrial pacing is contraindicated in patients with an A-V conduction disturbance.
- ATP therapy is contraindicated in patients with an accessory antegrade pathway.

IV. Warnings and Precautions

Delete this section and just state:

Please refer to the device labeling for a list of warnings and precautions

Sterilization, Storage, and Handling

- Contents of sterile package – The sterile package contains one implantable Medtronic AT500 device, and one torque wrench.
- Temperature limits – Store and transport the package between -18°C (0°F) to 55°C (131°F).
- "Use by" date – Do not implant the Medtronic AT500 device after the "Use by" date, because the battery's longevity could be reduced.
- Dropped device – Do not implant the device if it has been dropped on a hard surface from a height of 30 cm (12 in) or more after removal from its packaging.
- Checking and opening the package – Before opening the sterile package tray visually check for any signs of damage that might invalidate the sterility of its contents. Return damaged packages to the manufacturer. For instructions on opening the sterile package, see the diagram inside the lid of the shelf box.
- FOR SINGLE USE ONLY. – Do not resterilize or re-implant an explanted Medtronic AT500 device.
- Explant and disposal – Return explanted devices to Medtronic for analysis and disposal. See the back cover for mailing addresses.

Resterilization – Medtronic has sterilized the device package contents with ethylene oxide prior to shipment. Resterilization is necessary only if the seal on the

sterile package is broken. (Resterilization does not affect the "Use By" date.) If necessary, resterilize with ethylene oxide using a validated sterilization process, observing the following precautions:

- Do not resterilize using an autoclave, gamma radiation, organic cleaning agents (such as alcohol, acetone, etc.), or ultrasonic cleaners.
- Do not resterilize more than twice.
- Do not exceed 55 °C (131 °F) or 103 kPa (15 psi) when sterilizing.
- Store the resterilized components for an appropriate period to permit aeration of ethylene oxide gas.

Lead Evaluation and Lead Connection

Connector compatibility – Do no use any lead with this pacemaker without first verifying connector compatibility. Using incompatible leads can damage the connector or result in a leaking or intermittent connection.

Hex wrench – Do not use a hex wrench with a blue handle or a right-angle hex wrench. These wrenches have torque capabilities greater than is designed for the lead connector.

Device Operation

Fixed bipolar operation – Use of unipolar leads will result in loss of pacing output and sensing.

Rate responsive modes – Do not use rate responsive modes in those patients who cannot tolerate pacing rates above the programmed Lower Rate.

Single chamber atrial modes – Do not use single chamber atrial modes in patients with impaired AV nodal conduction because ventricular capture cannot be assured.

Pacing and sensing safety margins – Consider lead maturation when choosing pacing amplitudes, pacing pulse widths, and sensing levels.

Shipping values – Do not use shipping values for pacing amplitude and sensitivity without verifying that they provide adequate safety margins for the patient.

Electrical reset – Electrical reset is indicated by a programmer warning message displayed immediately upon interrogation. To restore the pacemaker to its previous operation it must be reset and reprogrammed.

Crosstalk – Crosstalk occurs in dual chamber pacemakers when atrial pacing output pulses are sensed by the ventricular lead. Crosstalk results in self-inhibition and is more likely to occur at high sensor-driven pacing rates, high atrial amplitudes, and wide atrial pulse widths. To prevent self-inhibition caused by crosstalk, program Ventricular Safety Pacing (VSP) on.

Slow retrograde conduction – Slow retrograde conduction, especially with conduction time greater than 400 ms, may induce pacemaker-mediated tachycardia (PMT).

Use of a magnet – Positioning a magnet or the programming head over the implanted Medtronic AT500 device suspends detection and treatment of atrial tachyarrhythmias. The magnet does not alter bradycardia therapy or initiate a Threshold Margin Test.

End of life (EOL) – Replace the Medtronic AT500 ™ device when the programmer displays an ERI or EOL message, and a battery voltage of 2.60 volts or less.

Oversensing during telemetry – Telemetry communication with the device may cause inappropriate sensed events, resulting in a brief inhibition of bradycardia therapy. Removing the programming head restores the device to normal operation.

Telemetry – Exposure to EMI may briefly interrupt programming and/or telemetry operations. Any successful interrogation or programming verifies proper communication between device and programmer.

Testing for cross-stimulation – At implant, and periodically when ATP therapy is enabled, perform testing at the programmed ATP output settings to ensure that ventricular capture does not occur. This is particularly important when the lead is placed in the inferior atrium.

Anti-coagulation - Use of the pacemaker should not change the application of established anti-coagulation protocols.

Rate control - Decisions regarding rate controls should not be based on the ability of the pacemaker to prevent atrial arrhythmias.

Pacemaker-dependent Patients

Diagnostic modes – Never program diagnostic modes (ODO) for pacemaker-dependent patients. For such patients, use the programmer's Inhibit function for brief interruption of outputs.

Inhibit function – Exercise caution when using the programmer to inhibit pacing (for example, to obtain an EGM of the patient's intrinsic activity) because the patient is without pacing support when the Inhibit function is in use.

Ventricular Safety Pacing (VSP) – Always program VSP on for pacemaker-dependent patients.

Medical Therapy Hazards

Diathermy – People with metal implants such as pacemakers, implantable cardioverter defibrillators (ICDs), and accompanying leads should not receive

diathermy treatment. The interaction between the implant and diathermy can cause tissue damage, fibrillation, or damage to the device components, which could result in serious injury, loss of therapy, and/or the need to reprogram or replace the device.

Electrosurgical cautery – Electrosurgical cautery could induce ventricular arrhythmias and/or fibrillation, or may cause device malfunction or damage. If electrocautery cannot be avoided, observe the following precautions:

- Use a bipolar electrocautery system, where possible.
- Have temporary pacing and defibrillation equipment available.
- Program the device to the DOO mode.
- Use short, intermittent, and irregular bursts at the lowest feasible energy levels.
- Avoid direct contact with the device or leads. If monopolar cautery is used, position the ground plate so that the current pathway does not pass through or near the device system.

External defibrillation – External defibrillation may damage the device or may result in temporary and/or permanent myocardial damage at the electrode tissue interface as well as temporary or permanent elevated pacing thresholds. Follow these precautions when using external defibrillation on a patient with an implanted cardiac device:

- Position defibrillation paddles as far from the implanted device as possible (minimum of 13 cm (5 in)), and perpendicular to the implanted device-lead system.
- Use the lowest clinically appropriate energy output.

High-energy radiation – High radiation sources such as cobalt 60 or gamma radiation should not be directed at the implanted device. If a patient requires radiation therapy in the vicinity of the implanted device, place lead shielding over the device to prevent radiation damage and confirm its function after treatment.

Lithotripsy – Lithotripsy may permanently damage the implanted device if it is at the focal point of the lithotripsy beam. If lithotripsy must be used, keep the implanted device at least 2.5 to 5.0 cm (1 to 2 in) from the focal point of the lithotripsy beam.

Magnetic resonance imaging (MRI) – Magnetic Resonance Imaging (MRI) should not be used on patients who have an implanted cardiac device because of the potential damage to the implanted device.

Radio frequency (RF) ablation – Radio frequency ablation procedure in a patient with an implanted cardiac device could cause device malfunction or damage. RF ablation risks can be minimized by:

- Have a Medtronic programmer available for temporary pacing.

- Program tachyarrhythmia detection **Off**.
- Program a non-rate responsive, asynchronous pacing mode prior to the procedure.
- Avoid direct contact between the ablation catheter and the implanted lead or device.
- Position the ground plate so that the current pathway does not pass through or near the device system.
- Have defibrillation equipment available.

Therapeutic ultrasound – Exposure of the device to therapeutic ultrasound is not recommended as it may permanently damage the device. Damage to the device may affect therapy.

Home and Occupational Environments

Patients should be directed to avoid devices that generate strong electric or magnetic interference (EMI). EMI could cause inappropriate pacing inhibition, malfunction, or damage resulting in non-detection or delivery of unneeded therapy. Moving away from the interference source, or turning it off, usually allows the device to return to its normal mode of operation.

High voltage lines – High voltage power transmission lines could generate enough EMI to interfere with device operation if approached too closely.

Communication equipment – Communication equipment such as microwave transmitters, line power amplifiers, or high power amateur transmitters could generate enough EMI to interfere with device operation if approached too closely.

Commercial electrical equipment – Commercial electrical equipment such as arc welders, induction furnaces, or resistance welders could generate enough EMI to interfere with device operation if approached too closely.

Home appliances – Home appliances which are in good working order and properly grounded do not usually produce enough EMI to interfere with device operation. There are reports of device disturbances caused by electrical hand tools or electric razors used directly over the device implant site.

Static magnetic fields – Patients should avoid equipment or situations where they would be exposed to static magnetic fields (greater than 10 gauss or 1 millitesla) since it could suspend detection. Examples of magnetic sources that could interfere with normal device operation include: stereo speakers, bingo wand, extractor wand, magnetic badges, or magnetic therapy products.

Electronic article surveillance (EAS) – Electronic Article Surveillance (EAS) equipment such as retail theft prevention systems may interact with the implanted device. Patients should be advised to walk directly through, and not to remain near an EAS system longer than is necessary.

Cellular phones – Hand-held cellular phones do not need any special precautions if you have a Medtronic AT500 device. For portable and mobile cellular phones that transmit above 3 watts, keep the telephone antenna 12 in (30 cm) away from the implanted device.

Tips to keep these distances:

Medtronic AT500 devices contain a filter that prevents most cellular phone transmissions from interacting with device operation. To further minimize the possibility of interaction, observe the following cautions:

- Hold the phone to the ear opposite the side of the implanted device.
- When carrying the phone, keep it in a location opposite the side of the implanted device. (When a cell phone is in the "listen" or "standby" mode, it can still send a signal).

Table 1. Cellular Phone Transmission Technologies

Transmission Technology	Frequency Range (MHz)
Analog	
FM (Frequency Modulation)	824 – 849
Digital TDMA[a] North American Standards	
TDMA – 11 Hz	806 - 821
NADC[b] TDMA - 50 Hz	824 – 849
PCS[c] 1900	1850 – 1910
Digital TDMA International Standards	
GSM[d]	880 - 915
DCS[e] 1800	1710 – 1785
Digital CDMA	
CDMA – DS[f]	824 - 849

[a] Time Division Multiple Access
[b] North American Digital Cellular
[c] Personal Communication System
[d] Global System for Mobile Communications
[e] Digital Cellular System
[f] Code Division Multiple Access - Direct Sequence

VI. Adverse Events

Potential Adverse Events

Adverse events (in alphabetical order), including those reported in Table 2 and Table 4, associated with pacing systems may include, but are not limited to:

- Cardiac perforation
- Cardiac tamponade
- Death
- Erosion through the skin
- Hematoma/seroma
- Infection
- Improper operation caused by the electronic article surveillance systems
- Myopotential sensing
- Nerve and/or muscle stimulation
- Pacemaker syndrome
- Rejection phenomena
  (local tissue reaction, fibrotic tissue formation, pacemaker migration)
- Threshold elevation

AT500 DDDRP Pacing System Clinical Studies

Two clinical studies are used to demonstrate safety and efficacy of the Medtronic AT500 DDDRP Pacing System and they are as follows:

- ATTEST – Atrial Therapy Efficacy and Safety Trial
- ASPECT – Atrial Septal Pacing Efficacy Clinical Trial

ATTEST Observed Adverse Events

For the ATTEST clinical study, reference Table 2 for a summary of all adverse events.

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Table 2. Adverse Event Summary – ATTEST

Adverse Event Type	Brady+AT/AF Patients		All Patients		Total
	Complications[1]	Observations[1]	Complications	Observations	
System/Procedure Related	45 (40 Pts)	218 (153 Pts)	57 (49 Pts)	263 (185 Pts)	320 (208 Pts)
Non-System/ Procedure Related	188 (136 Pts)	1461 (334 Pts)	251[2] (168 Pts)	1740[2] (385 Pts)	1991 (399 Pts)
Total	**233 (162 Pts)**	**1679 (341 Pts)**	**308 (198 Pts)**	**2003 (395 Pts)**	**2311 (413 Pts)**

[1] A complication is defined as an adverse event requiring invasive measures to correct; a therapy is considered invasive if it penetrates the skin, excluding the administration of parenteral fluids or drugs. An observation is defined as an adverse event that is resolved using only non-invasive measures.

[2] Includes adverse events categorized as "Unknown."

Table 3 is a listing of the system/procedure related adverse events for the ATTEST study. Of the 2311 events reported, 320 were system/procedure related.

Table 3. ATTEST System/Procedure Related Adverse Event Listing

Primary Condition	Complications		Observations		Total	
	Events	Patients* (%)	Events	Patients* (%)	Events	Patients* (%)
Atrial Flutter/Fibrillation Paroxysmal	2	2 (0.5)	5	5 (1.2)	7	7 (1.6)
Atrial Flutter/Fibrillation Persistent	0	0 (0)	2	2 (0.5)	2	2 (0.5)
Atrial Tachycardia	0	0 (0)	2	2 (0.5)	2	2 (0.5)
Back Pain/ Discomfort	0	0 (0)	2	2 (0.5)	2	2 (0.5)
Cardiac Perforation (Ventricular)	1	1 (0.2)	0	0 (0)	1	1 (0.2)
Chest Pain- Angina	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Chest Pain - non-cardiac	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Congestive Heart Failure	0	0 (0)	3	3 (0.7)	3	3 (0.7)
Cross-talk (non-persistent)	0	0 (0)	2	2 (0.5)	2	2 (0.5)
Daily Atrial Lead Check	0	0 (0)	24	22 (5.2)	24	22 (5.2)
Dizziness	0	0 (0)	3	3 (0.7)	3	3 (0.7)
Drug Related	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Dyspnea/ Shortness of Breath	0	0 (0)	4	4 (0.9)	4	4 (0.9)
Elevated Pacing Thresholds Atrial	0	0 (0)	2	2 (0.5)	2	2 (0.5)
Elevated Pacing Thresholds Ventricle	2	1 (0.2)	3	3 (0.7)	5	4 (0.9)
Emotional Distress	0	0 (0)	3	3 (0.7)	3	3 (0.7)
Failure To Capture/Loss Of Capture Atrial	0	0 (0)	3	3 (0.7)	3	3 (0.7)

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Primary Condition	Complications		Observations		Total	
	Events	Patients* (%)	Events	Patients* (%)	Events	Patients* (%)
Failure To Capture/Loss Of Capture Ventricle	1	1 (0.2)	1	1 (0.2)	2	2 (0.5)
Far-Field R-Wave Sensing	3	3 (0.7)	9	8 (1.9)	12	11 (2.6)
Fatigue/tiredness	1	1 (0.2)	1	1 (0.2)	2	2 (0.5)
Headache	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Hypotension	0	0 (0)	2	2 (0.5)	2	2 (0.5)
Inadequate Lead Pacemaker connection	2	2 (0.5)	0	0 (0)	2	2 (0.5)
Inappropriate programming	0	0 (0)	5	5 (1.2)	5	5 (1.2)
Lead Dislodgment Atrial	18	17 (4.0)	0	0 (0)	18	17 (4.0)
Lead Dislodgment Ventricle	5	5 (1.2)	0	0 (0)	5	5 (1.2)
Lead Insertion/Route Problem	2	2 (0.5)	2	2 (0.5)	4	4 (0.9)
Lead Insulation Failure	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Loss Of Sensing Intermittent	1	1 (0.2)	8	8 (1.9)	9	9 (2.1)
Loss Of Sensing Permanent	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Migration of pulse generator	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Musculoskeletal pain	0	0 (0)	2	2 (0.5)	2	2 (0.5)
Nausea	1	1 (0.2)	2	2 (0.5)	3	3 (0.7)
Near Syncope	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Other Conditions	3	3 (0.7)	20	20 (4.7)	23	23 (5.4)
Other Oversensing	0	0 (0)	6	6 (1.4)	6	6 (1.4)
Pacemaker-Mediated Tachycardia	0	0 (0)	3	3 (0.7)	3	3 (0.7)
Pain at pocket site	0	0 (0)	45	40 (9.4)	45	40 (9.4)
Palpitations	0	0 (0)	14	13 (3.0)	14	13 (3.0)
Pericardial Effusion	4	4 (0.9)	5	5 (1.2)	9	9 (2.1)
Peripheral Edema	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Phrenic Nerve/Diaphragm Muscle Stimulation Atrial	0	0 (0)	4	4 (0.9)	4	4 (0.9)
Phrenic Never/Diaphragm Muscle Stimulation Ventricle	4	4 (0.9)	1	1 (0.2)	5	5 (1.2)
Pleural Effusion	0	0 (0)	4	4 (0.9)	4	4 (0.9)
Pneumonia	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Pneumothorax as Result of Implant Procedure	2	2 (0.5)	6	6 (1.4)	8	8 (1.9)
Pocket Hematoma	1	1 (0.2)	17	17 (4.0)	18	18 (4.2)
Pocket Infection	1	1 (0.2)	10	10 (2.3)	11	10 (2.3)
Pocket Seroma	0	0 (0)	4	4 (0.9)	4	4 (0.9)

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Primary Condition	Complications		Observations		Total	
	Events	Patients* (%)	Events	Patients* (%)	Events	Patients* (%)
Pocket Stimulation	0	0 (0)	3	3 (0.7)	3	3 (0.7)
Puncture of Subclavian artery	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Shoulder pain/ discomfort	0	0 (0)	2	2 (0.5)	2	2 (0.5)
Sleep problems	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Suspected pacemaker failure	1	1 (0.2)	5	4 (0.9)	6	5 (1.2)
Suspected Programmer Or Software Failure	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Swelling of pocket site	2	2 (0.5)	7	7 (1.6)	9	9 (2.1)
Thrombosis	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Upper pacing rate too slow	0	0 (0)	1	1 (0.23)	1	1 (0.23)
Upper respiratory symptom	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Ventricular Tachycardia Non-Sustained	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Ventricular tachycardia (Sustained)	0	0 (0)	1	1 (0.2)	1	1 (0.2)
Total	**57**	**49 (11.5)**	**263**	**185 (43.3)**	**320**	**208 (48.7)**

*Note for the patient totals that some patients had events in more than one category.

ATTEST VT/VF Observations

Ten sustained VT/VF episodes were reported in four patients. The investigator classification and adverse event committee review did not indicate that any of the VT/VF episodes were caused by prevention pacing or ATP therapies.

ATTEST Patient Discontinuations

Lost to Follow-up forms were received for 19 patients. Six patients requested withdrawal from the study. Two forms were submitted at the time of patient's death.

ATTEST Patients Requiring Device Explant

A total of eight patients required device explant during the study period. Two patients received replacement AT500; two patients were not re-implanted with a pulse generator. Two patients required replacement with an ICD as a result of inducible sustained ventricular tachycardia. One patient was implanted with a Medtronic Kappa pulse generator as a result of a random component failure in the AT500 and one patient was implanted with an InSync 8040 pacemaker.

ATTEST Patient Deaths

Over the course of the study, 43 patients expired. For these deaths, neither the investigator nor the Adverse Event Advisory Committee attributed the cause of death to the AT500 system. The causes of death were cardiac arrest (7), congestive heart failure (7), cardiopulmonary arrest (5), renal failure (3), myocardial infarction (3), pulmonary arrest (3), sepsis (2), cardiogenic shock (2), cardiomyopathy, ventricular arrhythmia, perforation of superior vena cava, aspiration pneumonitis, intracerebral hemorrhage, atherosclerotic heart disease, emphysema, brain cancer, leukemia, pneumonia, and one death of unknown cause.

ASPECT Observed Adverse Events

For the ASPECT clinical study, reference Table 4 for a summary of all adverse events.

Table 4. Adverse Event Summary – ASPECT

Adverse Event Type	Septal (n=148)		Non-Septal (n=150)		Total
	Complications*	Observations*	Complications	Observations	
System/Procedure-Related	21 (19 Pts)	68 (55 Pts)	23 (21 Pts)	66 (50 Pts)	178 (127 Pts)
Non-System/ Procedure Related	72 (56 Pts)	252 (106 Pts)	75 (54 Pts)	244 (112 Pts)	643 (235 Pts)
Total	**93 (66 Pts)**	**320 (121 Pts)**	**98 (68 Pts)**	**310 (121 Pts)**	**821 (261 Pts)**

* A complication is defined as an adverse event requiring invasive measures to correct; a therapy is considered invasive if it penetrates the skin, excluding the administration of parenteral fluids or drugs. An observation is defined as an adverse event that is resolved using only non-invasive measures.

Table 5 lists the system/procedure related adverse events for the ASPECT study. Of the 821 events reported, 178 were system or procedure related.

Table 5. ASPECT System/Procedure Related Adverse Event Listing

Primary Condition	Complications		Observations		Total	
	Events	Patients* (%)	Events	Patients* (%)	Events	Patients* (%)
Allergic Reaction	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Anxiety	0	0 (0)	2	2 (0.67)	2	2 (0.67)
Atrial Flutter/Fibrillation Paroxysmal	1	1 (0.34)	16	15 (5.03)	17	16 (5.37)
Atrial Flutter/Fibrillation Persistent	0	0 (0)	2	2 (0.67)	2	2 (0.67)
Aware of Pacing System	0	0 (0)	3	3 (1.01)	3	3 (1.01)
Belching	0	0 (0)	2	1 (0.34)	2	1 (0.34)
Chest Muscle Stimulation	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Chest Pain - non-cardiac	0	0 (0)	3	3 (1.01)	3	3 (1.01)
Chronic Obstructive Pulmonary Disease	1	1 (0.34)	0	0 (0)	1	1 (0.34)

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Primary Condition	Complications		Observations		Total	
	Events	Patients* (%)	Events	Patients* (%)	Events	Patients* (%)
Congestive Heart Failure	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Cough	0	0 (0)	1	1 0.34)	1	1 (0.34)
Daily Atrial Lead Check Failure	0	0 (0)	10	7 (2.35)	10	7 (2.35)
Delayed Ventricular Pace	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Deep Vein Thrombosis	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Dyspnea/Shortness of Breath	0	0 (0)	2	2 (0.67)	2	2 (0.67)
Edema	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Electromagnetic Interference Sensing	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Elevated Pacing Thresholds Atrial	0	0 (0)	3	3 (1.01)	3	3 (1.01)
Elevated Pacing Thresholds Ventricle	3	3 (1.01)	4	4 (1.34)	7	7 (2.35)
Endocarditis	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Failure To Capture/Loss Of Capture Atrial	1	1 (0.34)	1	1 (0.34)	2	2 (0.67)
Failure To Capture/Loss Of Capture Ventricle	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Failure To Position The Lead At The Atrial Septum	0	0 (0)	1	1 (0.34)	1	1 (0.34)
False Rejection of Episodes Due To FFRW Criterion	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Far-Field R-Wave Sensing	0	0 (0)	4	4 (1.34)	4	4 (1.34)
Fatigue/tiredness	0	0 (0)	2	2 (0.67)	2	2 (0.67)
Inappropriate Programming	0	0 (0)	3	3 (1.01)	3	3 (1.01)
Incision Problem	0	0 (0)	5	5 (1.68)	5	5 (1.68)
Insufficient Slack in Atrial and Ventricular Leads	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Lead Dislodgment Atrial	7	7 (2.35)	2	2 (0.67)	9	9 (3.02)
Lead Dislodgment Ventricle	6	6 (2.01)	0	0 (0)	6	6 (2.01)
Lead Insertion/Route Problem	0	0 (0)	3	3 (1.01)	3	3 (1.01)
Loss Of Sensing Intermittent	0	0 (0)	4	4 (1.34)	4	4 (1.34)
Migration of lead	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Muscular Stimulation	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Nausea	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Other Oversensing	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Pacemaker Syndrome	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Pacemaker-Conducted Atrial Tachyarrhythmia	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Pacemaker-Mediated Tachycardia	0	0 (0)	9	8 (2.68)	9	8 (2.68)
Pain	0	0 (0)	14	14 (4.70)	14	14 (4.70)
Palpitations	0	0 (0)	3	3 (1.01)	3	3 (1.01)

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Primary Condition	Complications		Observations		Total	
	Events	Patients* (%)	Events	Patients* (%)	Events	Patients* (%)
Patient Activator Malfunction	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Pericardial Effusion	2	2 (0.67)	0	0 (0)	2	2 (0.67)
Phrenic Nerve/Diaphragm Muscle Stimulation Atrial	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Phrenic Never/Diaphragm Muscle Stimulation Ventricle	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Pneumothorax As Result Of The Implant Procedure	5	5 (1.68)	0	0 (0)	5	5 (1.68)
Pocket Hematoma	3	3 (1.01)	12	12 (4.03)	15	15 (5.03)
Pocket Infection	1	1 (0.34)	2	2 (0.67)	3	3 (1.01)
Pocket Site Opened	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Presyncope	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Skin Rash	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Stroke/CVA/TIA	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Subclavian Vein Perforation	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Suspected Lead Conductor Fracture Ventricle	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Suspected Programmer Or Software Failure	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Swelling Of Pocket Site	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Syncope	1	1 (0.34)	1	1 (0.34)	2	2 (0.67)
Thrombosis	0	0 (0)	1	1 (0.34)	1	1 (0.34)
Thrombosis Formation At Lead Ventricle	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Ventricular Fibrillation	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Ventricular Tachycardia Non-Sustained	1	1 (0.34)	0	0 (0)	1	1 (0.34)
Total	**44**	**40 (13.40)**	**134**	**105 (35.20)**	**178**	**127 (42.60)**

*Note for the patient totals that some patients had events in more than one category.

ASPECT VT/VF Observations

Three sustained VT/VF episodes were reported in three patients. The investigator classification and adverse event committee review did not indicate that any of the VT/VF episodes were caused by prevention pacing or ATP therapies.

ASPECT Patient Discontinuations

Six patients requested withdrawal from the study. Four of them were never implanted with an AT500 and requested withdrawal. Two patients in Europe requested withdrawal after refusing to come to the investigator for follow-up visits.

ASPECT Patients Requiring Device Explant

Over the course of the study, eleven devices were explanted for reasons including worsening of congestive heart failure (five patients), ventricular fibrillation, MAZE procedure, endocarditis, pericardial effusion, and infection (two patients). Two devices were replaced with AT500 devices. Two devices were not replaced. Five devices were replaced with biventricular pacing devices, one device was replaced with an ICD, and one device was replaced with a Medtronic Kappa pulse generator.

ASPECT Patient Deaths

There were 17 patient deaths recorded in the study; all but one were determined to be non-system related by the investigator and the Adverse Event Advisory Committee. For one death it was unknown if it was related to the system since the patient, whose cause of death was congestive heart failure, was cremated before an explant or autopsy could be performed. Causes of death included congestive heart failure (4 patients), cancer (2 patients), cerebral vascular accident, myocardial infarction, coronary artery disease, cardiomegaly, respiratory failure, anoxic encephalopathy, acute heart failure, cardiac cachexy, cardiopulmonary arrest, cardiac arrhythmia and one death of unknown cause.

VII. Alternative Practices and Procedures

While surgery or drug therapy may be alternatives to cardiac pacing in certain instances, cardiac pacing is often the standard treatment for the indications described above. Other commercially available single chamber or dual chamber pacemakers provide alternatives to the AT500.

VIII.Marketing History

The Medtronic AT500 DDDRP pacing system is currently distributed commercially outside the United States. Specifically, this product is approved for sale in Canada, Australia and the European Community. This device has not been withdrawn from the market in any country for any reason related to the safety and effectiveness of the device.

IX. Summary of Preclinical Studies

Nonclinical Laboratory Testing

Nonclinical testing of the Medtronic AT500 DDDRP pacing system was conducted to ensure that the components and the finished device perform in accordance with their design specifications.

Integrated Circuit

Electrical testing of each IC was performed on a sample of 77 units. Electrical stability of the IC was assessed through accelerated life testing. Each unit was stressed at 150°C for 184 hours minimum. Electrical testing of each IC was conducted prior to life testing, and following life testing using a mixed signal automated test system verifying significant performance parameters of the pacing system environment. There were no failures observed during the 184 hour life test, and no significant shifts in the electrical performance of any of the critical parameters were observed over the 184 hour life test.

Hybrid

Electrical qualification testing was performed on a sample of 149 hybrids. Electrical stability of the hybrid module was assessed through accelerated life testing. Each unit was stressed at 2.55V and 125°C for a minimum of 77000 device hours. Electrical testing of each hybrid was conducted prior to life testing, and after life testing using a computerized electronic test system verifying significant performance parameters of the pacing system environment. There were no design related failures observed during the77000 device hours life test, and there were no significant shifts in the electrical performance of any of the critical parameters due to design or manufacturing over the 77000 device hours.

Testing indicated that there were no design-related failures during the qualification testing. Electrical test data showed no trend that would affect the stability of the final product performance. All qualification activities indicate that the Hybrid Circuitry is of acceptable quality and reliability for use in the AT500.

Battery Testing

The AT500 utilizes one power source, the Delta 30H lithium hybrid cathode medium-rate cell. The battery was subjected to Accelerated Discharge (64 samples), Application Discharge (8 samples) and Environmental Tests (16 samples).

All the Accelerated Discharge test samples exceeded the specified requirements.

The 1.0 mA test results easily exceed the capacity to ERI and ERI to EOL requirements. At the 30μA rate, the results also easily exceed the capacity to ERI requirements.

The Environmental Test results show normal and expected behavior for the Delta 30H lithium hybrid cathode medium-rate cell batteries.

Current Drain Characterization

Current Drain Characterization for the AT500 was performed at the hybrid level (1 hybrid), and measured current drain over various environmental and device conditions. All test results were within specification.

Connector Testing

The AT500 uses one connector assembly: IS-1 bipolar. The IS-1 bipolar connector is the same connector used on the Medtronic Thera-*i*[5] and Medtronic Kappa 700/600[6] series family of pulse generators and did not require requalification.

Environmental and Mechanical Testing

Environmental and mechanical qualification testing was performed with 22 samples. Additionally, characterization tests were performed using various quantities of test samples. Test devices were subjected to the following tests:

[5] Thera-i (P890003/S37, Approved 31 Oct 1995)

[6] Kappa 700/600 (P980035, Approved 29 Jan 1999)

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Table 6. Mechanical Qualification and Characterization Tests

	Test	Objective	Method	Number of Test Samples	Test Results
1.	Temperature Storage	Verify the device will withstand extreme temperatures experienced in a normal handling and distribution environment. This is a qualification test.	Devices are exposed to a minimum of 6 hours at -18° C. This is followed by a minimum 6 hour exposure at +55° C with a 1 hour stabilization at room temperature between exposures.	22	Passed
2.	Mechanical Vibration	Verify the device will withstand vibration frequencies experienced in a normal handling and distribution environment. This is a qualification test.	Devices are subjected to vibration in three 15 minute cycles in each of 3 orthogonal axes. The frequency of vibration sweeps from 5 to 500 to 5 Hz with a 2.5G acceleration.	22	Passed
3.	Mechanical Shock	Verify that the device will function safely after mechanical shock impacts experienced in normal handling and distribution environment. This is a qualification test.	Devices are subjected to a minimum change in velocity of 118 inches/second with a 1 millisecond Haversine wave form in each of three orthogonal axes (six positions). This shock equates to an effective free fall height of 18 inches.	22	Passed
4.	Temperature Shock	Determine if devices will withstand extreme and rapid temperature changes. This is a characterization test.	Devices are exposed to ten cycles of air-to-air thermal shock at -40° C and +65° C. Transition time between temperatures is less than one minute. Dwell at each temperature extreme is 1 hour.	4	Passed

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	Test	Objective	Method	Number of Test Samples	Test Results
5.	Increasing Heights Mechanical Shock	Determine if devices can withstand extreme mechanical shocks. This is a characterization test.	Devices are exposed to mechanical shocks at effective heights starting at 24 inches and increasing to 60 inches in 6 inch increments (7 heights). Three orthogonal axes in two orientations are tested for a total of six applications at each height (Total of 42 shocks).	4	Passed
6.	Mechanical 20G Vibration	Determine if devices will withstand extreme mechanical vibration. This is a characterization test.	Devices are subjected to the 20G Italian Standard Vibration test consisting of a 30 minute cycle from 10-to-500-to-10 Hz at 20G acceleration with a displacement of 8 mm along each of three orthogonal axes with a crossover-to-constant acceleration at 35 Hz.	4	Passed
7.	Mechanical (Dimensional) Specifications	Verify the devices meet requirements for mechanical dimensions, mass, and volume. This is a qualification test.	Physical measurements are recorded. Mass is determined by triple beam balance and volume by liquid displacement.	10	Passed
8.	Telemetry Mapping	Evaluate the performance of telemetry uplink and downlink. This is a characterization test.	A RF head is incrementally positioned in the space around a device to map the space where successful interrogations with the device occur.	2	Passed

	Test	Objective	Method	Number of Test Samples	Test Results
9.	Destructive Analysis	Verify device did not experience any damage to components, solder joints, wire bonds, hybrid, or battery during mechanical qualification or characterization tests. Inspect workmanship of hybrid and pulse generator assembly.	Visually inspect pulse generator shield, shield weld, and lead connector for damage, dents, cracks.	5	Passed

Full functionality of each device was verified at the completion of all environmental and mechanical tests. All testing passed.

Parameter Stability

Testing was performed on the AT500 to determine the stability of the device pacing parameters when exposed to varying environmental conditions. Sensitivity, amplitude, accelerometer interface, pace current detector and capture detector were evaluated under varying load impedance, and supply (battery) voltage conditions. The test results demonstrate that the device parameters met specifications and remained stable under varying pacing load and supply voltage conditions.

Packaging Qualification

With the exception of the inner tray, the AT500 package design is identical to those designed for other Tachy products (e.g, Gem[7]). Qualification testing for the packaging configuration consisted of a) environmental stress tests including extreme vibration, stacking, and drop testing, and b) visual inspection of sterile package seals and package materials and contents. All 22 of the AT500 inner tray packages tested met the package design test requirements.

FMEA/System Hazard Analysis

Utilizing both a fault tree analysis and a Failure Mode and Effects Analysis (FMEA) approach, a complete analysis of the device and hybrid microcircuit has been performed on all critical components included in the AT500. A systems hazard analysis was performed to assess the design and development processes of the pacing system to ensure that critical failures modes or potentially hazard situations have been identified and adequately eliminated or mitigated.

[7] Gem (P980016, Approved 09 October 1998)

Animal Testing

A canine study was conducted to verify the function and performance of the Medtronic AT500 DDDRP pacing system. The primary objectives of this study were to demonstrate the expected operation of the AT500, including proper performance in dual chamber pacing modes, Modeswitching, Atrial Rate Stabilization and Atrial Preference Pacing features, Arrhythmia detection, therapy delivery, and rate response performance. In summary, the sensing/pacing operation of the device, Modeswitching and device performance during treadmill operation performed as expected. The arrhythmia detection algorithms and atrial anti-tachy pacing feature also performed appropriately and as expected.

This animal study was conducted in compliance with the Good Laboratory Practices (GLP) Regulation 21 CFR Part 58.

Firmware Testing

The firmware for AT500 was developed in accordance with applicable Medtronic development processes. Three levels of testing were performed on the firmware, including unit, integration and verification testing. All tests passed.

Software Validation

The AT500 application software (Model 9968) was developed and tested in accordance with Medtronic's formal procedures for software development and testing. These procedures include development of a Software Requirements Specification, a detailed design specification, a Hazard Analysis, a retest strategy, and a Verification Test Specification. The software was tested per the Verification Test Specification. Errors, anomalies, and inconsistencies were noted in Software Change Reports and all issues resolved.

Following final retest of the software, a final configuration audit was performed by Software Quality Engineering to ensure that all documents and code were properly controlled and released.

System Testing

System Testing of Medtronic AT500 DDDRP pacing system evaluated use of pulse generators with programmer, Medtronic Vision software, AT500 application software (Model 9968) and Medtronic patient activator/assistant to assure their operation is within the limits of their respective specifications. Issues associated with the technical literature and/or software were identified and resolved during testing.

Electromagnetic Compatibility (EMC) and Cell Phone Testing

Electromagnetic Compatibility (EMC) testing was performed using a minimum of twenty-two (22) pulse generators (where appropriate). The test devices were subjected to radiated electric fields (pulsed radiated and continuous wave), sinusoidal currents, electrosurgical cautery currents, X-ray compatibility, and transthoracic (high level) defibrillation pulses. In addition, characterizational testing was performed subjecting the devices to cellular phone transmission frequencies.

The AT500 was found to meet performance specifications for exposure to radiated electric fields. When subjected to sinusoidal currents, no devices were observed to exhibit rates above or below the specified test tolerances, and the pulse amplitude and duration of all devices were observed to remain within acceptable tolerances. Electrosurgical cautery testing demonstrated that the AT500 meets all EMC compatibility requirements. ICD compatibility testing consisted of exposing the pulse generators to ICD discharges to ensure the pulse generator does not experience electrical resets. All devices tested remained fully functional and met the testing requirements. The second type of ICD testing consisted of exposing the pulse generator to highenergy discharges used for defibrillation therapies. No anomalies were observed in the devices tested. However, it should be noted that the AT500 is contraindicated for implantation with an ICD. The AT500 was found to meet the performance specifications for devices exposed to in-vitro transthoracic defibrillation currents and no anomalies were observed during testing. Cell phones were tested per CDRH "In-Vitro Pacemaker EMI Test Protocol for Cellular Phones." No anomalies were observed while testing eight different analog and digital cellular phones in different modulation modes and frequencies.

Biocompatibility Testing

The materials used in the AT500 that are directly exposed to body tissue and/or fluids are titanium, silicone rubber, silicone rubber adhesive, and polyurethane. These materials have all been used in Medtronic pulse generators for several years and have an established history of biocompatibility through long-term human use. In addition to long-term human use, the materials listed have been previously tested for biocompatibility per the Medtronic submissions referenced herein.

Medtronic certifies that all of the direct and indirect tissue contacting materials used to fabricate the AT500 are identical to the Medtronic Kappa 700/600 devices, as they were approved on January 29, 1999, (PMA Document Control No. P980035), in formulation, processing and sterilization, and no other chemicals have been added (e.g. plasticizers, fillers, coloring agents, mold release agents, cleaning agents, etc.), with the exception of Parylene C coating which is not used for the AT500.

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Conclusion Drawn from Nonclinical Laboratory Tests

Medtronic conducted a system hazard analysis on all new features and critical components and then conducted testing to evaluate these and other device features. All test results were found to be acceptable.

X. Summary of Clinical Studies

Two clinical studies are used to demonstrate safety and efficacy of the Medtronic AT500 DDDRP Pacing System and they are as follows:

- ATTEST – Atrial Therapy Efficacy and Safety Trial
- ASPECT – Atrial Septal Pacing Efficacy Clinical Trial

Reference Table 7 for additional information.

Table 7. Overview of Clinical Studies

Study	Cohort	No. of Patients Enrolled	Cumulative No. of Device Months	Average No. of Device Months/ Patient	No. of Implant-ing Centers	First Implant Date	Data Cut-off Date
ATTEST	Brady +AT/AF	370	6447	17.4	28	18 Oct 1999	26 April 2002
	Other Brady	57	1113	19.5			
ASPECT	Brady +AT/AF	298	5330	18.1	37	01 Sept 1999	26 April 2002

ATTEST Clinical Study

Design of Study

The ATTEST clinical study was a multi-center (28 implanting centers worldwide), prospective, randomized, parallel group, two-sample, single-blinded design performed to characterize the safety and effectiveness of the Medtronic AT500 DDDRP pacing system. Patients with or without a history of atrial tachyarrhythmias (AT/AF) were enrolled in the study. The location for placement of the atrial lead was left to the discretion of the investigator for patients indicated for a dual-chamber pacemaker. Reference Figure 1 for a description of the clinical study design.

To evaluate effectiveness of the atrial prevention (Atrial Preference Pacing (APP), Atrial Rate Stabilization (ARS) and Post Mode Switch Overdrive Pacing (PMOP)) and termination therapies (Atrial Antitachycardia Pacing (ATP)), all patients were stratified based on the presence or absence of documented history of AT/AF at enrollment. Patients with a documented history of AT/AF were categorized as Brady +AT/AF, and the patients without a documented history of AT/AF were categorized as Other Brady.

Patients were randomized to having prevention and termination therapies either all ON or all OFF at the one-month follow-up. A three-month evaluation period followed the randomization. Upon completion of the four-month follow-up visit, the protocol allowed the AT500 to be programmed according to the physician's preference.

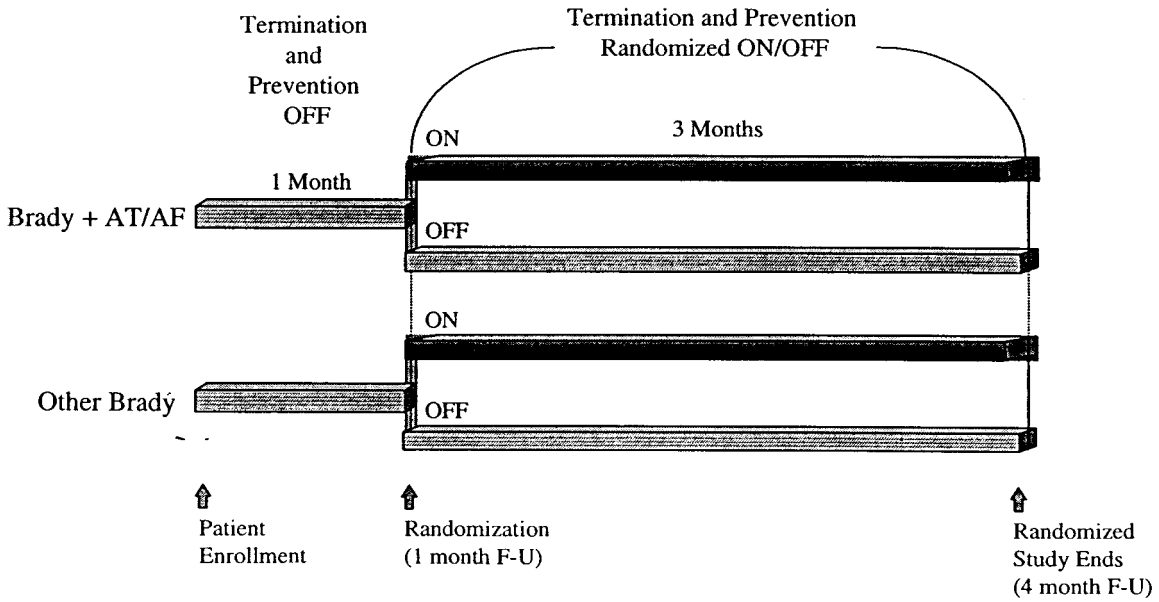

Figure 1. ATTEST Clinical Study Design

ATTEST – Patient Assessment

Patients enrolled into the study represented a general dual chamber pacing population, as specified by the ACC/AHA guidelines for pacing indications. A total of 427 patients were enrolled and 424 were implanted. Of these patients, 370 were enrolled in the Brady +AT/AF group and the remaining 57 were enrolled in the Other Brady group. Three patients were not implanted with an AT500. Ventricular lead placement was not possible for two patients; one expired as a result of complications during the AT500 implant procedure prior to implantation of the device.

Primary Objectives

- To establish the safety of the AT500 system as demonstrated by freedom from system/procedure related complications at three months post-implant.
- Two measures of effectiveness of AT/AF prevention and termination therapies were evaluated:
  - Demonstration of the effectiveness of the prevention and termination therapies in reducing the frequency of spontaneous AT/AF episodes by 30%.
  - Demonstration of the effectiveness of the AT500 prevention and termination therapies in reducing the burden of spontaneous AT/AF episodes by 30%.

Secondary Objectives

- To estimate the accuracy (positive predictive value) of the atrial tachyarrhythmia detection algorithm in classification of atrial tachyarrhythmias (AT/AF).
- To characterize the effectiveness of ATP in terminating spontaneous AT/AF episodes.
- To characterize the potential reduction of frequency and burden in patients who had no documented history of atrial tachyarrhythmias at enrollment.
- To demonstrate the impact of the AT500 system on patients' quality of life as measured by the SF-36 Health Survey and Symptom Checklist.
- To characterize the pacing and sensing performance of the AT500 system using the Medtronic DR180 digital Holter recorder.
- To characterize the effect of prevention and termination therapies on the frequency of symptomatic episodes of atrial tachyarrhythmias (AT/AF).

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ATTEST – Demographic Data

The mean age of the total population was 70.0 years; the mean age of the Brady+AT/AF population was 69.9 years. Male patients comprised 54.6% of the Brady+AT/AF group and 54.3% of all patients were male.

Table 8. Patient Demographics – ATTEST

	Brady+AT/AF (N=370)	Other Brady (N=57)	All (N=427)
Gender (N,%)			
Male	202 (54.6%)	30 (52.6%)	232 (54.3%)
Female	168 (45.4%)	27 (47.4%)	195 (45.7%)
Age (years)			
Mean	69.9	70.5	70.0
Range	10.0 - 98.0	13.0 - 90.0	10.0 - 98.0
Standard deviation	12.9	16.1	13.4
Primary Indication (mutually exclusive, N, %)			
Acquired AV Block	42 (11.4%)	27 (47.4%)	69 (16.2%)
Chronic Bi/tri-fascicular Block	2 (0.5%)	2 (3.5%)	4 (0.9%)
AV Block with Acute MI	2 (0.5%)	--	2 (0.5%)
Sinus Node Dysfunction	267 (72.2%)	24 (42.1%)	291 (68.1%)
Prevention and Termination of Tachy	45 (12.2%)	1 (1.8%)	46 (10.8%)
Other	12 (3.2%)	3 (5.3%)	15 (3.5%)

ATTEST – Data Analysis and Results

Accumulating 7561 device months of experience, the performance of the Medtronic AT500 DDDRP pacing system was found to meet or exceed all safety objectives as shown in Table 9. The rate of complications was found to be similar to that observed in Medtronic studies of pacemakers that are commercially available.

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Table 9. Results of Primary Objectives – ATTEST

Primary Objectives:	Results:
Safety (n=427) **Hypothesis:** 3 Month System / Procedure-Related Complication-Free Survival Greater than 80% – All Patients	40 patients experienced their first system/procedure-related complication through 3 months of follow-up Complication Free Survival Probability: 90.3% **95% Lower Confidence Bound: 87.7% (> 80%)**
Effectiveness: AT/AF Frequency Reduction, AT/AF Burden Reduction **Hypothesis:** The frequency of AT/AF episodes with prevention and termination ON will be at least 30% less than the frequency with prevention and termination OFF.	For patients in the efficacy cohort of the Brady+AT/AF group, the median frequency in the ON arm was 0.043 episodes/day and in the OFF arm it was 0.039 episodes/day. The median burden in the ON arm was 0.136 hrs/day and in the OFF arm it was 0.037 hrs/day. **The difference between arms was not statistically significant for either frequency or burden.**

Table 10. Results of Secondary Objectives – ATTEST

Secondary Objectives:	Results:
Accuracy (positive predictive value) of appropriately detecting atrial tachyarrhythmias	According to investigator classifications, the positive predictive value for detection of atrial arrhythmias was 98%.
Effectiveness of terminating spontaneous AT/AF episodes	ATP therapies effectively terminated 53.3% of all treated episodes based on crude estimates and 40.8% when adjusted using the Generalized Estimating Equations methodology.
Reduction of frequency and burden in patients who had no history of atrial tachyarrhythmias at enrollment	No statistically significant difference was found in frequency and burden comparisons between treatment groups in the Other Brady patient group.
Patients' quality of life as measured by the SF-36 Health Survey and Symptom Checklist	As measured by the SF-36 and the Symptom Checklist, there was no statistically significant difference in quality of life between the ON and OFF groups at Baseline and 4-months. However, quality of life of all patients improved from Baseline to 4-months, and at 4 months patients in both groups scored in the normal range for the age-matched population at large.[8]
Pacing and sensing performance using the DR180 digital Holter recorder.	One hundred five (105) Holter recordings were reviewed from 66 patients to characterize pacing and sensing performance of the AT500. The Holter recordings confirm that the AT500 operated as expected.
Frequency of symptomatic AT/AF episodes	The ON group had a frequency of 0.057 symptomatic episodes per day, while the OFF group had a frequency of 0.064 symptomatic episodes per day. There was no statistically significant difference in frequency of symptomatic episodes between ON and OFF treatment groups.

[8] Ware JE, Snow KK, Kosinski M et al. SF-36 Health Survey Manual and Interpretation Guide. QualityMetric Incorporated, Lincoln, RI, 2000,pg 7:15.

ATTEST – Device Failures and Replacement

There was one device failure reported as part of the ATTEST Clinical study. This device was explanted as a result of a ventricle sense failure. The device was returned to Medtronic for further analysis. Analyses indicated that this was a random component failure caused by a resistive leakage in the pre-amp of the L292 IC.

ASPECT Clinical Study

Design of Study

The ASPECT clinical study was a multi-center (37 implanting centers worldwide), prospective, randomized, single-blinded, cross-over design performed to investigate the safety and efficacy of the Medtronic AT500 DDDRP pacing system and its atrial arrhythmia prevention pacing features with specific atrial lead placement. Patients were candidates for a standard pacemaker and had a history of symptomatic atrial tachyarrhythmia. Lead placement sites included septal and non-septal atrial pacing sites.

This study was a prospective evaluation of the following features of the Medtronic AT500 DDDRP Pacing System: Atrial Preference Pacing (APP), Atrial Rate Stabilization (ARS) and Post Mode Switch Overdrive Pacing (PMOP). Patient data was collected at implant, pre-discharge, one month, four month, and seven months post implant.

At implant, patients were randomized to either a septal or non-septal atrial lead site placement. A second randomization was performed for prevention pacing features (APP, ARS, PMOP) ON-OFF vs. OFF-ON crossover periods at the one-month follow-up. The crossover period was 3 months, with the first 2 weeks of each crossover period considered a stabilization period to account for atrial remodeling effects. Data from the 2-week stabilization period was not utilized for the efficacy objectives. Data was collected at the end of each crossover period of 3 months (See Figure 2).

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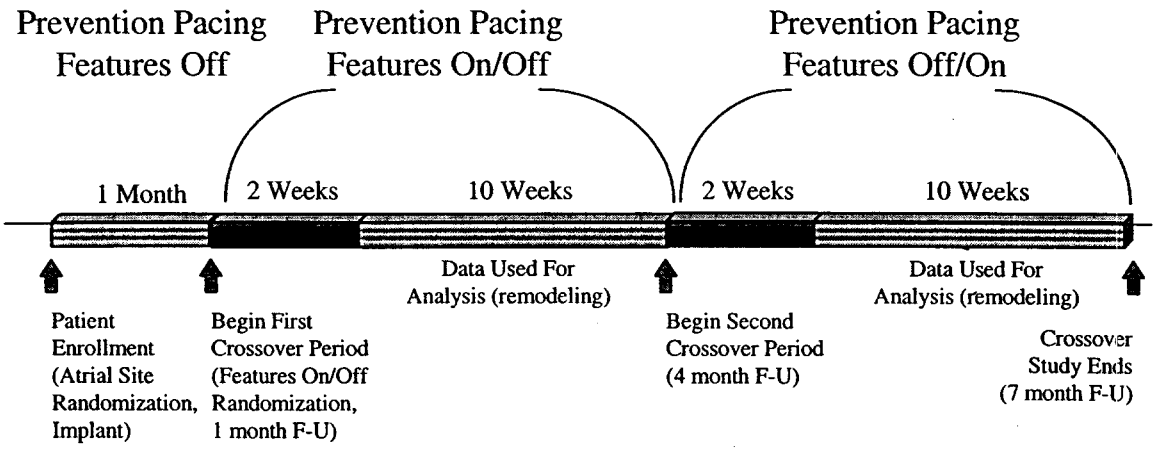

Figure 2. ASPECT Clinical Study Design

ASPECT – Patient Assessment

Patients enrolled into the study represented a general dual chamber pacing population, as specified by the ACC/AHA guidelines for pacing indications. A total of 298 patients were enrolled and 294 were implanted. Of the four not implanted, one patient was discovered to be in permanent AF at implant, one patient was found to have 1:1 conducted sinus tachycardia at implant, one patient had high atrial thresholds at implant, and one patient could not be transferred to the study center after enrollment.

Primary Objectives

- To establish the safety of the AT500 system as demonstrated by freedom from system/procedure related complications at three months post-implant.
- To establish the safety of atrial leads when used in the septal pacing site as demonstrated by freedom from atrial lead related adverse events at three months post-implant.
- To demonstrate that the prevention pacing features reduce atrial tachyarrhythmia frequency by at least 30% in at least 50% of patients when used in conjunction with an atrial septal pacing site.
- To demonstrate that the proportion of patients with at least a 30% reduction in frequency in the septal site (prevention pacing features ON vs. OFF) will be greater than the proportion in the non-septal site (prevention pacing features ON vs. OFF).

Secondary Objectives

- To observe the performance of the prevention pacing features during Holter monitoring.
- To characterize the electrical performance (pulse width thresholds at 2.0V, sensing thresholds, and lead impedance) of atrial leads over time.

- To characterize the effect that the prevention pacing features have on atrial tachyarrhythmia burden in the septal and non-septal atrial pacing sites.
- To characterize the effect the prevention pacing features have on patient quality of life in the septal and non-septal atrial pacing sites.
- To characterize the effect that the prevention pacing features have on the frequency of symptomatic episodes of atrial tachyarrhythmias in the septal and non-septal atrial pacing sites.
- To characterize the effect that the prevention pacing features have on the frequency of premature atrial contractions in the septal and non-septal atrial pacing sites.
- To characterize the placement of an atrial lead in the septal pacing site.

ASPECT – Demographic Data

Information regarding patient demographics and cardiovascular history is presented in Table 11. The mean age of the 298 enrolled patients was 69.6 years. There were 182 males (61.1%) and 116 females (38.9%) in the ASPECT study. The patients' indications for pacemaker implants are also shown in Table 11.

Table 11. Patient Characteristics at Enrollment – ASPECT

Patient Characteristics	Septal (N=148)	Non-Septal (N=150)	Total (N=298)
Gender (N,%)			
Male	91 (61.5%)	91 (60.7%)	182 (61.1%)
Female	57 (38.5%)	59 (39.3%)	116 (38.9%)
Age (years)			
Mean	68.6	70.7	69.6
Range	42.6 - 87.5	45.4 – 88.5	42.6 - 88.5
Standard deviation	10.1	9.5	9.9
Primary Indication (N,%) (mutually exclusive)			
Acquired AV Block	18 (12.2%)	18 (12.0%)	36 (12.1%)
Chronic Bi/Tri-fascicular Block	3 (2.0%)	2 (1.3%)	5 (1.7%)
Sinus Node Dysfunction	104 (70.3%)	103 (68.7%)	207 (69.5%)
Other	23 (15.5%)	27 (18.0%)	50 (16.8%)

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ASPECT – Data Analysis and Results

Accumulating 5330.3 device months of experience, the performance of the AT500 was found to meet or exceed all safety objectives as shown in Table 12. The rate of complications was found to be similar to that observed in Medtronic studies of pacemakers that are commercially available.

Table 12. Results of Primary Objectives – ASPECT

Primary Objectives:	Results:
Safety (n=298) **Hypothesis:** 3 Month System / Procedure-Related Complication-Free Survival Greater than 80%	37 patients experienced their first system/procedure-related complication through 3 months of follow-up Complication-Free Survival Probability: 87.4% **95% Lower Confidence Bound: 84.3% (> 80 %)**
Safety of atrial leads when used in septal sites (n=148 septal, 150 non-septal) **Hypothesis:** Difference in 3 Month Atrial Lead-Related Event-Free Survival of Septal and Non-Septal Leads is <10%	11 septal patients and 7 non-septal patients experienced their first atrial lead related adverse event through three months of follow-up Event Free Survival Probability (Septal): 92.5% 95% Confidence Interval (Septal): (88.3%, 96.8%) Event Free Survival Probability (Non-septal): 95.3% 95% Confidence Interval (Non-septal): (92.0%, 98.8%) **95% Upper Confidence Bound (difference in survival rate): 7.5% (< 10 %)**
Effectiveness: AT/AF Frequency Reduction with an Atrial Septal Pacing Site **Hypothesis:** The proportion of patients with a significant (at least 30%) reduction in frequency of AT/AF episodes with prevention pacing ON vs. OFF must be at least 50%.	In the atrial septal patients in the efficacy cohort, 30.7% of patients had 30% or greater reduction of frequency in the ON period as compared to the OFF period of the study with a one-sided 95% lower confidence bound of 21.9%. **The proportion of septal patients with a 30% or greater reduction in frequency was not at least 50% (the a priori objective performance criterion).**
Effectiveness: AT/AF Frequency Reduction for Septal Compared to Non-Septal Patients **Hypothesis:** The proportion of patients with a significant (at least 30%) reduction in frequency of AT/AF episodes in the septal site (prevention pacing features ON vs. OFF) will be greater than the proportion in the non-septal site (prevention pacing features ON vs. OFF).	The proportion of patients with non-septal atrial leads who had 30% or greater reduction in frequency in the ON period as compared to the OFF period was 32.2%, and the proportion of patients with septal atrial leads who had a 30% or greater frequency reduction was 30.7%. **The proportion of septal patients with a frequency reduction of at least 30% was not significantly greater than the percent of non-septal patients with at least 30% frequency reduction.**

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Table 13. Results of Secondary Objectives – ASPECT

Secondary Objectives:	Results:
Observation of the performance of prevention pacing features during Holter monitoring.	At the one-month follow-up, 20 patients with septal atrial lead implants and 22 patients with non-septal atrial lead implants were Holter monitored for 24 hours with the prevention features ON. Analysis of the Holter recordings showed that all evaluated features operated as expected and there were no differences noted between septal and non-septal patients.
Electrical performance of the atrial leads.	Pulse width thresholds, sensing thresholds, and lead impedance were measured for both septal and non-septal patients from implant through seven months. The electrical performance of the leads was not significantly different in the septal and non-septal groups.
Atrial tachyarrhythmia burden in septal and non-septal pacing sites.	For patients in the efficacy cohort, in the septal site, the median difference in burden between the ON and OFF periods was not significantly different from zero. In the non-septal site, the median difference in burden was also not significantly different from zero. The change in burden for the septal group was not significantly different from the corresponding change in the non-septal group.
Quality of Life in septal and non-septal pacing sites.	For patients in the efficacy cohort, as measured by the SF-36 Health Survey, patients in both the septal and non-septal arms had no significant difference in quality of life scores for prevention pacing features ON vs. OFF. All patients scored in the normal range for the age-matched population at large during both the ON and OFF crossover periods.[7] Similarly, the Symptom Checklist measurements had no significant difference in the number of symptoms, symptom frequency, or symptom severity for patients in both the septal and non-septal arms with prevention pacing features ON vs. OFF.
Frequency of symptomatic episodes of atrial tachyarrhythmias in septal and non-septal pacing sites	For patients in the efficacy cohort, in the septal site, the mean difference in symptomatic episodes between the ON and OFF periods was -1.1 episodes/month (1.4 episodes/month ON versus 2.5 episodes/month OFF), which is significantly different from zero ($p=0.013$); in the non-septal site, the mean difference in symptomatic episodes was not significantly different from zero.
Frequency of premature atrial contractions in septal and non-septal atrial pacing sites.	For patients that were in the efficacy cohort, in the septal site, the median difference in PACs for ON - OFF was –202.5.0 PACs/day, which was not significantly different from zero ($p=0.073$). In the non-septal site, the median difference in PACs for ON - OFF was –273.3 PACs/day, which was significantly different from zero ($p<0.001$). The change in PACs for the septal group was not significantly different from the corresponding change in the non-septal group.
Atrial lead placement.	There were 148 patients randomized to the septal atrial lead site. Of these, 136 (91.9%) were placed in the septal site. Of the 12 patients who were not placed in the septal site as randomized, four were never implanted with an AT500, four were mechanically unable to reach and fixate on the septum (failure to implant AT500 was not related to septal lead randomization), two were unable to find acceptable thresholds on the septum, one discovered after implant that the lead was not on the septum, and one abandoned septal positioning for a medical reason. In addition, after implant, two patients with septal lead placement had lead dislodgements resulting in a repositioning of the lead to a non-septal position because the physician mechanically unable to reach and fixate on the septum. Of the 150 leads randomized to the non-septal site, 150 (100%) were placed as randomized.

ASPECT – Prevention Pacing and Percentage Atrial Pacing

The prevention pacing features (APP, ARS and PMOP) were observed to increase the percentage of atrial pacing while minimizing increase in atrial rate. The atrial pacing percentage increased from 69.0% with prevention pacing features OFF to 95.5% with prevention pacing features ON. The average atrial rate increased only slightly, from 72 ppm with prevention pacing features OFF to 77 ppm with prevention pacing features ON.

ASPECT – Reduction in symptomatic episode burden

The prevention pacing features were observed to reduce the burden of symptomatic episodes in patients with an atrial septal lead placement. Burden was defined, *post hoc*, as the number of symptomatic days divided by the number of total days of follow up. A symptomatic day was a day in which a symptomatic episode was reported by the patient. For all patients with atrial septal lead placement (N=125), the burden of symptomatic episodes was 4.48% when the prevention features were OFF compared to 2.76% when the prevention features were ON, for a 38.4% reduction ($p = 0.0043$).

ASPECT – Device Failures and Replacement

There were no device failures reported as part of the ASPECT Clinical study.

Compassionate Use Device Clinical Experience

To date, there have also been 41 compassionate uses implants of the Medtronic AT500 system. The compassionate use experience has a similar safety profile to the ATTEST and ASPECT clinical studies.

Gender Bias

A standard epidemiological approach was used to assess the poolability of data with respect to gender. The results of the analyses show no statistically significant associations between the primary objectives and gender so the results presented are representative of both genders.

XI. Conclusions Drawn from Studies

The Medtronic AT500 introduces incremental features for the treatment of atrial arrhythmias. These include atrial arrhythmia termination features, atrial pacing features, and enhanced diagnostic features. Bench, animal and clinical data support the safety and effectiveness of these features when used in combination in this device, as indicated in the labeling.

In vitro testing, consisting of component-level testing, device testing, system testing, and *in vivo* animal studies, demonstrate the proper operation of the AT500 system. This testing provides reasonable assurance that the device is safe and performs as intended.

Clinical studies have demonstrated that the AT500 has an adequate overall safety profile. The device appropriately detects atrial arrhythmias. Atrial arrhythmia termination therapies are appropriately delivered, successfully terminate atrial arrhythmia episodes, and do not induce ventricular arrhythmias. The combination of atrial termination and atrial pacing features do not have a significant effect on the amount of time patients spent in atrial arrhythmias or the number of episodes experienced. The results of the clinical study suggest that the atrial pacing features, by themselves, significantly increase the percentage of atrial pacing. When the atrial pacing features alone are looked at in terms of the percentage of symptomatic days, a reduction was observed in patients with the atrial septal lead placement.

XII. Panel Recommendation

Pursuant to section 515(c)(2) of the Food, Drug and Cosmetic Act (the Act) as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to Circulatory System Devices Panel, and FDA Advisory Panel, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH Decision

The results of the preclinical and clinical studies demonstrated that the new design features, when used as indicated in the labeling, are safe and effective.

FDA found Medtronic's manufacturing facility to be in compliance with the Device Quality System Regulation, (21 CFR part 820). CDRH issued an approval order on March 26, 2003.

XIV. Approval Specifications

Directions for use: See product labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the Labeling.

Post-approval Requirements and Restrictions: See approval order.